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MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
SKIBINSKY, ANNA	

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/685,737	RUBIN ET AL.	
	Examiner	Art Unit	
	Anna Skibinsky	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Applicant's

Applicant's amendments to claims 40 and 43 are acknowledged. Claims 40-43 are under examination.

Double Patenting

1. The rejection of claims 40-43 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4-6 of U.S. Patent No. 6,759,206 is withdrawn in view of the terminal disclaimer filed 6/08/2007.

Claim Rejections - 35 USC § 101

The rejection of claims 40-43 under 35 U.S.C. 101 is withdrawn in view of Applicant's Amendments/Remarks filed 6/08/2007.

Claim Rejections - 35 USC § 112

The rejection of claim(s) 43 for being Vague and Indefinite under 35 USC § 112-2nd paragraph is withdrawn in view of Applicant's Remarks/Amendments filed 6/08/2007.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marks et al. (US Patent 6,794,128) in view of Proffitt et al. (Cytometery, vol. 24 (1996) pages 204-213).

The instant claims are drawn to a machine readable storage medium comprising a program containing instructions for measuring internalization of cell surface proteins through a cell screening system.

1. Claim 40 recites identifying internalized cell surface receptor proteins in cells where individual cells comprise at least a first luminescent reporter molecule that reports on the cell surface receptor and at least a second luminescent reporter molecule that reports on cells. Internalized cell surface receptors are identified by determining a luminescent signal from the first reporter molecule that surpasses a user defined intensity.

2. Marks et al. teach a method of internalizing phages into target cells and identifying the internalized phages (Abstract). The prior art teaches a method of identifying internalizing antibodies and internalizing receptor ligands (col. 1, lines 20-26, col. 3, lines 17-25). This includes identifying internalizing antibodies as well as internalizing receptors (col. 1, lines 20-25). The method can be carried out by labeling the phage with a reporter gene encoding a fluorescent protein such as GFP or a luciferase (col. 2, line 66 to col. 3, line 5; and col. 4, lines 9-12).

3. Marks et al. teaches a method of identifying internalized receptors (col. 13, lines 44-55) as well as using reporter genes to identify cells that express GFP. This method can be used to identify target cells (col. 17, line 45 to col. 18, line 22) within a subtractive cell line (col. 18, lines 23-65). Here, the subtractive cells display all the markers of the target cell except the marker (e.g. receptor) that is to act as a target for the desired binding of antibodies or binding polypeptides. This reads on the limitations set forth in claim 40(a) where each cell is contacted with at least two reporter molecules.

4. Marks et al. goes on to teach identification of an internalized phage (col. 19, line 57 to col. 20, line 10) with the use of a detectable fluorescent signal where the phage bears a marker (e.g. label) and the surface bound or internalized phages are sorted (col. 20, lines 3-14).

5. The prior art of Marks et al. teaches the measuring of internalized phages with FAC (fluorescence activated cell sorting) (col. 46, lines 47-48; col. 47, line 65 to col. 48, line 3; and Figure 9). This reads on the limitations set forth in claim 40(b) where

calculations on cells that have internalized the luminescently labeled reporter molecule are performed.

6. Claim 40, step (c) recites displaying data on internalized cell surface receptor proteins.

7. Marks et al. teaches a table containing data on cell surface bound phage and internalized phage (col. 29, Table 4).

8. Claim 41 recites the steps (a) and (b) carried out at multiple time points. As illustrated in Figure 9, the internalization of the phages are calculated at multiple time points.

9. Claim 42 recites determining an aggregate area of the objects that represent the internalized cell surface receptor protein (step (i)) and a number of objects that represent the internalized cell surface receptor protein (step (iv)).

10. Marks teaches that the methods of the prior art invention can be used to identify internalizing receptors and regions of the receptor that when bound induce internalization of the binding moiety (col. 3, lines 17-20), as in claim 41, step (i). Marks further teaches the identifying of internalized members of the phage display library if the members are internalized into one or more of the target cells (col. 3, lines 38-40).

11. Marks does not teach calculating a number and or percent of the individual cells that internalized the at least first luminescently labeled reporter molecule. Marks also does not teach a machine readable storage medium comprising a program that executes procedures for measuring internalization of cell surface receptor proteins.

12. Proffitt et al. however teaches a computerized scanning system and algorithm (page 207, col. 1, ¶ 3) that is able to measure the relative cell numbers (page 204, col. 1, lines 1-4) that contain a fluorescent label. The total relative fluorescence intensity for the entire well containing cells is determined, "which is proportional to cell number" (page 207, col. 1, ¶4 to col. 2, ¶ 1). Figure 3 shows the number of cells per well.

13. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have the procedure of labeling antibodies and bacteriophages that are internalized by a cell with a fluorescent proteins as taught by Marks and then measuring the number of cells that had the internalized fluorescent protein with the computerized scanning system as taught by Proffitt et al. One of skill in the art would have been motivated to use the cell quantifying fluorescently labeled cells as taught by Proffitt et al. to measure the internalization of cell surface receptors as taught by Marks because Proffitt et al. teaches that this is an effective method of determining which cells are viable cells (i.e. cells that are alive not dead) (page 211, col. 1, ¶1). One of skill in the art would have had a reasonable expectation of success at utilizing the computerized scanning system that determines the number of fluorescing cells taught by Proffitt et al. with the assays of internalized reporter molecules as taught by Marks because Marks teaches using fluorescent proteins and wherein the system of Proffitt et al. measures fluorescence.

RESPONSE TO ARGUMENTS

14. Applicant's arguments filed 6/08/2007 have been fully considered but they are not persuasive.

15. Applicants argue that Marks does not teach methods for identifying internalizing receptors (Remarks page 5, ¶ 6 to page 6, ¶ 1).

16. In response and as noted by Applicants themselves (Remarks, page 6, lines 1-6), Marks' disclosure teaches that when the antibody or bacteriophage binds to a receptor, the receptor internalizes together with the antibody or bacteriophage (col. 1, lines 20-25). The teaching of Marks is well within the scope of claim 40 because claim 40 recites "identifying internalized cell surface receptor proteins". Thus, when the internalized antibody or bacteriophage that bound to the receptor is identified, this indicates the identification of the internalized cell surface receptor. The claim does not require that the first luminescent marker be bound directly to the internalized cell surface receptor protein. The claim only requires that that the first luminescent reporter molecule **report on** a cell surface receptor protein of interest, which is achieved by the teachings of Marks.

17. Applicants argue (Remarks, page 6, lines 6-12) that Marks does not teach a program containing a set of instructions to cause a cell screening system to measure internalization of cell surface receptor proteins and carry out the method of claim 40.

18. In response, Marks in view of Proffitt et al. do teach the instant limitation wherein Proffitt et al. teach the computerized system cells screening system that includes a

scanning algorithm (page 207, col. 1, ¶3)) and software (page 206, col. 2) that measure the relative number of cells that contain fluorescent labels.

19. Applicants argue (page 6, lines 13-21) that the Marks' teaching of calculating a number or percentage of individual cells that internalized the labeled reporter molecule (that reports on cell surface receptor protein of interest) is misplaced and that Marks does not teach a measure of cell surface receptor protein internalization.

20. In response, Marks in view of Proffitt et al. do teach the instant limitation wherein Proffitt et al. teach the quantification of the number of cells that fluoresce (page 207, section "Quantificaiton of Fluoresence").

3. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marks in view of Proffitt et al. as applied to claims 40-42 above, and further in view of Dunlay et al. (US Patent 5,989,835, in IDS filed 5/19/04).

4. Marks et al. in view of Proffitt et al. make obvious the identification of internalized receptors wherein the cells contain internalized green fluorescent proteins that report on cells that contain the internalized receptors and wherein Proffitt et al. teach a computerized scanning system that scans and quantifies the fluorescence in cells to determine the number of cells. Internalizing antibodies in an affinity matrix or solid support are at taught Marks (col. 13, lines 56-62) as required by claims 40-42. However, Mark and Proffitt et al. do not teach the images of the array to obtain both low and high resolution images of those array locations that contain internalized cell surface receptor proteins.

5. Dunlay et al. teach providing cells containing fluorescent reporter molecules in an array of locations and scanning numerous cells in each location with a fluorescent microscope (Abstract). The whole area of the plate can be imaged (col. 1, lines 32-37) where cells have been treated with fluorescent reagents such as GFP and expressing GFP in cells for use as reporter molecules (col. 2, lines 11-53). Further Dunlay et al. teach imaging the array of cells at a low resolution and imaging particular locations in the microplate at a higher resolution (col. 5, lines 19-27).

6. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have implemented the imaging technique of Dunlay et al. to image the cells with internalized GFP reporter molecules that report on internalized receptors as taught by Marks and Proffitt. One of skill in the art would have been motivated to use the multi-resolution imaging technique of Dunlay et al. in the method to be performed by the computer readable media-contained instructions of Marks and Proffitt et al. because Dunlay et al teach that using two resolutions improves the overall throughput of the screening system (col. 4, lines 25-27).

RESPONSE TO ARGUMENTS

Applicant's arguments with respect to claims 40-43 have been considered but are moot in view of the new ground(s) of rejection above.

Applicants argue that Dunlay does not cure the deficiencies of Marks. It is noted that Marks in view of Proffitt in view of Dunaly do teach all of the limitations of the claims.

Conclusion

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Skibinsky whose telephone number is (571) 272-4373. The examiner can normally be reached on 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anna Skibinsky, PhD

MARJORIE A. MORAN
PRIMARY EXAMINER

9/12/07